PAKISTAN HEART JOURNAL ESTABLISHED 1968
OPEN ACCESS
P: ISSN: 0048-2706
E: ISSN: 2227-9199

Original Article

Comparison of Intracoronary Verapamil and Adenosine for No-Reflow in Normotensive Patients with Acute Coronary Syndrome: A Prospective Observational Study

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DOI: 10.47144/phj.v57i4.2787

Citation: Amin QNU, Rauf MA, Shah SHA, Shakir SU, Shah SKU, Ali A, Ali N. Comparison of Intracoronary Verapamil and Adenosine for No-Reflow in Normotensive Patients with Acute Coronary Syndrome: A Prospective Observational Study. Pak Heart J. 2024;57(04):[Ahead of Print].

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Conflict of interest: Authors declared no conflict of interest.

Funding: The author(s) received no specific funding for this work.

Double blinded peer review history:
Received: June 1, 2024
Review began: June 5, 2024
Revision received: September 1, 2024
Accepted: September 1, 2024

Abstract

Objectives: This study aimed to compare the efficacy of intracoronary verapamil versus adenosine in managing the no-reflow phenomenon in normotensive patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

Methodology: We conducted a prospective observational study at Hayatabad Medical Complex Peshawar from March 2023 to March 2024. A total of 150 normotensive ACS patients scheduled for PCI were enrolled and treated with either intracoronary verapamil (200 µg) or adenosine (48 µg) based on the clinical judgment of the treating cardiologist upon identifying the no-reflow phenomenon. The primary outcomes included improvements in myocardial perfusion, assessed by the achievement of TIMI III flow immediately and at 30 minutes via angiographic analysis. Secondary outcomes assessed were microvascular resistance (IMR), endothelial function (FMD), and the incidence of major adverse cardiac events (MACE) within six months.

Results: The verapamil group exhibited a higher percentage of patients achieving TIMI III flow post-treatment compared to the adenosine group (92% vs. 78%, p = 0.03). Both treatment groups demonstrated reductions in IMR (verapamil: 18.5 ± 2.8 units; adenosine: 19.1 ± 3.1 units, p = 0.29) and improvements in FMD (verapamil: 4.1 ± 0.5%; adenosine: 3.9 ± 0.6%, p = 0.15). The incidence of MACE was 18% in the verapamil group and 8% in the adenosine group, indicating comparable safety profiles for both agents.

Conclusion: Intracoronary verapamil and adenosine both effectively enhance myocardial perfusion and endothelial function in normotensive ACS patients following PCI. Verapamil showed a slight advantage in achieving TIMI III flow and reducing microvascular resistance, suggesting it may offer superior benefits in specific clinical scenarios. These results support the use of both agents in managing the no-reflow phenomenon, with potential preference for verapamil in particular contexts.

Keywords: Acute coronary syndrome (ACS), Percutaneous coronary intervention (PCI), No-reflow phenomenon, Intracoronary verapamil

INTRODUCTION

Acute coronary syndrome (ACS) encompasses a range of conditions arising from acute myocardial ischemia, typically due to an imbalance between the coronary blood supply and myocardial oxygen demand [1]. This term includes unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). ACS imposes a significant global health burden, characterized by high morbidity and mortality rates. During percutaneous coronary intervention (PCI) for ACS, one of the most challenging complications is the no-reflow phenomenon. This occurs when, despite the successful recanalization of epicardial coronary arteries, myocardial perfusion remains inadequate due to issues at the microcirculatory level, often not visible on standard angiography. The no-reflow phenomenon is associated with severe outcomes, including increased heart failure, arrhythmias, and mortality [2].

The pathophysiology of the no-reflow phenomenon involves several microvascular dysfunction mechanisms, such as microvascular spasm, endothelial swelling, capillary plugging, and ischemic injury [3]. These factors contribute to impaired blood flow at the microvascular level, which is not detectable by conventional angiography but has profound implications for patient prognosis. Understanding these mechanisms is crucial for developing effective strategies to prevent and manage the no-reflow phenomenon.

Among pharmacological approaches to counteract microvascular dysfunction, the intracoronary administration of verapamil and adenosine has emerged as a key therapeutic option. Verapamil, a calcium channel blocker, alleviates microvascular spasm by reducing calcium influx into vascular smooth muscle cells, thus promoting vasodilation and improving blood flow. Despite its potential benefits, verapamil's use is occasionally limited by its negative inotropic effects, which may be problematic in patients with compromised myocardial function [3].

Conversely, adenosine acts as a potent vasodilator through the stimulation of A2 receptors in the coronary vasculature, leading to rapid and effective dilation of the coronary microvasculature. Adenosine's short half-life allows for quick dosing adjustments, making it a flexible option for managing microvascular resistance during PCI [4]. Despite its advantages, adenosine's efficacy can vary among different patient populations, highlighting the need for direct comparative studies with other agents such as verapamil to establish more reliable treatment protocols [5,6].

Recent research underscores the necessity of understanding the comparative efficacy of these two agents, particularly in specific patient populations such as normotensive individuals with ACS—a group not extensively studied in prior research. This study aims to address this gap by systematically comparing the effects of intracoronary verapamil and adenosine on myocardial perfusion and endothelial function in normotensive ACS patients undergoing PCI. By focusing on this patient subgroup, the study seeks to elucidate the differential impacts of these pharmacological agents on microvascular resistance and endothelial health, thereby identifying the most effective treatment for managing the no-reflow phenomenon in normotensive ACS patients [7].

While both verapamil and adenosine are established in the treatment of no-reflow, this study is innovative in its focus on normotensive ACS patients, where optimal management strategies are less defined. Previous studies often included hypertensive or mixed populations, leaving a gap in the literature regarding the best approach for normotensive individuals. Additionally, the study employs advanced measures of microvascular resistance, such as the Index of Microcirculatory Resistance (IMR), and endothelial function, measured by flow-mediated dilation (FMD), to provide a more detailed understanding of the relative benefits of these agents. The results could lead to more targeted and effective treatment strategies, potentially improving clinical outcomes for patients undergoing PCI for ACS [8].

METHODOLOGY

Study Design: This study was designed as a prospective observational trial to evaluate the efficacy of intracoronary verapamil versus adenosine in improving myocardial perfusion during percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS). The primary focus was on assessing the improvement in TIMI flow grades, a key indicator of myocardial perfusion, immediately post-intervention and at a 30-minute follow-up.

Setting: The research was conducted at the Department of Cardiology, Hayatabad Medical Complex (HMC) Peshawar. This setting provided a comprehensive environment for monitoring and assessing PCI procedures and patient outcomes over a one-year period from March 2023 to March 2024.

Participants: The study included adults aged 18 years or older who were diagnosed with acute coronary syndrome (ACS) and required percutaneous coronary intervention (PCI). To qualify, patients needed to be normotensive, defined as having a systolic blood pressure between 120 and 130 mmHg and a diastolic blood pressure between 80 and 85 mmHg at the time of PCI. Exclusion criteria encompassed known hypersensitivity or contraindications to verapamil or adenosine, chronic renal failure (with serum creatinine levels exceeding 1.5 mg/dL), hemodynamic instability or cardiogenic shock, and a history of previous coronary bypass surgery. In total, 150 normotensive patients who met these criteria were enrolled. These participants were then allocated into two groups: one group of 75 patients received intracoronary verapamil, while the other group of 75 patients received adenosine.

Variables: The primary outcome variable for this study was the improvement in myocardial perfusion, which was assessed using the TIMI flow grade. This measure provided a direct evaluation of how well blood was flowing through the coronary arteries after the intervention. Secondary outcome variables included the measurement of microvascular resistance through the Index of Microcirculatory Resistance (IMR), which offered insights into the status of the microcirculation. Additionally, endothelial function was evaluated through flow-mediated dilation (FMD) of the brachial artery, both before and after PCI. The study also monitored major adverse cardiac events (MACE), including death, non-fatal myocardial infarction, or the need for repeat revascularization, within a six-month follow-up period.

Data Sources/Measurement: Data were collected from patient medical records, PCI procedural logs, and follow-up assessments. The TIMI flow grade was determined using standard angiographic techniques immediately following the intervention and at a 30-minute follow-up. IMR was measured using a pressure-wire technique, and FMD was assessed using high-resolution ultrasound. MACE were recorded during the six-month follow-up period through patient interviews and clinical record reviews.

Bias: To address potential biases, several measures were implemented. Selection bias was minimized by including all eligible normotensive ACS patients undergoing PCI during the study period, which ensured a representative sample of the patient population. Observer bias was mitigated through blinding during data collection and analysis phases, with standardized protocols applied consistently across all participating clinicians. To ensure comparability between the two groups, baseline characteristics were compared, and statistical adjustments were made for any imbalances that were identified.

Study Size: The sample size of 150 patients was determined based on prior studies evaluating intracoronary verapamil and adenosine in similar clinical contexts. The calculation aimed to achieve an 80% power with a significance level of 0.05, allowing for a robust comparison of outcomes between the verapamil and adenosine groups. Patients were evenly divided into two groups of 75 to ensure balanced comparisons.

Quantitative Variables: Continuous variables such as TIMI flow grades, IMR values, and FMD measurements were analyzed as means with standard deviations. These variables provided detailed insights into myocardial perfusion and vascular function.

Ethical Considerations: The study received approval from the Institutional Ethics Review Board at Hayatabad Medical Complex, Peshawar, under certificate number 1366. All participants provided written informed consent in accordance with the ethical guidelines outlined in the Declaration of Helsinki.

Statistical Methods: Data analysis was performed using SPSS version 25.0. Descriptive statistics were used to summarize demographic details and procedural data. Continuous variables were compared using independent t-tests, while categorical variables were analyzed using chi-square tests. A p-value of less than 0.05 was considered statistically significant. Statistical adjustments were made for any imbalances in baseline characteristics between the two groups.

RESULTS

Participants: The study included a total of 150 patients with acute coronary syndrome (ACS), who were undergoing percutaneous coronary intervention (PCI). Among these patients, 90 (60%) were diagnosed with ST-segment elevation myocardial infarction (STEMI), while the remaining 60 (40%) had non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. Participants were equally divided into two groups: 75 patients received intracoronary verapamil, and 75 received adenosine.

Descriptive Data: Table 1 provides an overview of the baseline characteristics of the participants in both treatment groups. The mean age of patients in the verapamil group was 60 ± 7 years, while in the adenosine group, it was 61 ± 8 years, with no significant difference between the groups (p = 0.45). The proportion of male patients was similar in both groups, with 54% in the verapamil group and 52% in the adenosine group (p = 0.83). Baseline TIMI scores were comparable, with a mean of 2.1 ± 0.8 in the verapamil group and 2.0 ± 0.9 in the adenosine group (p = 0.62). Index of Microcirculatory Resistance (IMR) values before treatment were also similar: 30.2 ± 4.5 units in the verapamil group and 29.8 ± 4.7 units in the adenosine group (p = 0.74). Flow-mediated dilation (FMD) percentages before PCI were 3.1 ± 0.6% in the verapamil group and 3.0 ± 0.7% in the adenosine group (p = 0.55).

Table 1: Patient Demographics and Baseline Characteristics

Variable	Verapamil (n=75)	Adenosine (n=75)	p-value
Age (years)	60 ± 7	61 ± 8	0.45
Sex (% Male)	54%	52%	0.83
Baseline TIMI	2.1 ± 0.8	2.0 ± 0.9	0.62
IMR Pre (units)	30.2 ± 4.5	29.8 ± 4.7	0.74
FMD Pre (%)	3.1 ± 0.6	3.0 ± 0.7	0.55

Note: Values are mean ± SD or percentages. TIMI - Thrombolysis In Myocardial Infarction, IMR - Index of Microcirculatory Resistance, FMD - Flow-Mediated Dilation

Outcome Data

Primary Outcome: TIMI Flow Grade Improvement
The mean post-treatment TIMI flow grade was significantly higher in the verapamil group (2.9 ± 0.3) compared to the adenosine group (2.7 ± 0.4) with a p-value of 0.03. This indicates that verapamil was more effective in improving myocardial perfusion compared to adenosine.

Secondary Outcomes:

- **Microvascular Resistance (IMR):** Post-treatment IMR values were slightly lower in the verapamil group (18.5 ± 2.8 units) compared to the adenosine group (19.1 ± 3.1 units). However, this difference was not statistically significant (p = 0.29), suggesting that both treatments had similar impacts on microvascular resistance.
- **Endothelial Function (FMD):** Endothelial function improved in both groups post-treatment. The verapamil group showed an increase in FMD from 3.1 ± 0.6% to 4.1 ± 0.5%, while the adenosine group increased from 3.0 ± 0.7% to 3.9 ± 0.6%. Despite the improvement, the difference between the groups was not statistically significant (p = 0.15), indicating comparable effects on endothelial function.

Table 2: Treatment Efficacy on Microvascular Resistance and Endothelial Function

Outcome	Verapamil (n=75)	Adenosine (n=75)	p-value
Post-Treatment TIMI	2.9 ± 0.3	2.7 ± 0.4	0.03
IMR Post (units)	18.5 ± 2.8	19.1 ± 3.1	0.29
FMD Post (%)	4.1 ± 0.5	3.9 ± 0.6	0.15

Note: Lower IMR Post values indicate better outcomes; higher FMD Post percentages indicate improved endothelial function.

Main Results: Major Adverse Cardiac Events (MACE): The incidence of major adverse cardiac events within six months following the procedure was 18% in the verapamil group and 8% in the adenosine group. This difference in MACE rates, as depicted in Figure 1 (right panel), was not statistically significant (p > 0.05), suggesting that both treatments have comparable safety profiles in terms of long-term outcomes.

DISCUSSION

This study provides a comparative analysis of the efficacy of intracoronary verapamil versus adenosine in managing the no-reflow phenomenon among normotensive patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Our findings indicate that while both pharmacological agents are effective, verapamil demonstrates a statistically significant advantage in improving TIMI flow grades, a critical measure of myocardial perfusion. This aligns with previous

research highlighting the benefits of verapamil in similar clinical scenarios.

Recent literature has underscored the role of intracoronary pharmacotherapy in enhancing coronary perfusion during PCI. Saif et al. [8], demonstrated that verapamil significantly improves coronary flow and reduces the incidence of no-reflow in ACS patients, which supports our study's findings. Similarly, Nguyen et al. [9] conducted a meta-analysis on adenosine's efficacy, revealing its effectiveness in mitigating microvascular obstruction and improving clinical outcomes. Although variability in patient response was noted, these results are consistent with our observation that both verapamil and adenosine effectively address myocardial perfusion issues, albeit with distinct nuances.

The observed improvement in TIMI flow grades with verapamil suggests that it may provide a more robust initial response in managing no-reflow, particularly in normotensive patients. This finding is consistent with Jaffe et al. [10], who reported similar enhancements in coronary flow using verapamil. Additionally, Khan et al. [6] compared intracoronary epinephrine and adenosine, highlighting adenosine's efficacy in specific clinical contexts. However, our study suggests that verapamil might offer a slight advantage in myocardial perfusion improvement, a topic that has not been extensively explored in existing literature.

Despite these promising results, several limitations warrant consideration. The observational design of the study introduces potential selection bias, as treatment allocation was determined by the treating cardiologist rather than randomization. This could have influenced the outcomes despite efforts to standardize data collection and minimize observer bias. Furthermore, while the sample size was sufficient for detecting differences in primary outcomes, it may not have been adequate to identify subtle differences in secondary outcomes. Additionally, the six-month follow-up period may limit our ability to capture long-term effects and complications associated with the use of these agents.

Our study evaluates the comparative efficacy of intracoronary verapamil and adenosine in addressing the no-reflow phenomenon in normotensive ACS patients undergoing PCI. The results offer valuable insights into the differential effects of these pharmacological agents and their implications for clinical practice. Verapamil was associated with a statistically significant improvement in post-treatment TIMI flow grades compared to adenosine (2.9 ± 0.3 vs. 2.7 ± 0.4, $p = 0.03$). Although verapamil showed a trend towards greater reduction in microvascular resistance (IMR) and slightly better improvement in endothelial function (FMD), these differences were not statistically significant. The incidence of major adverse cardiac events (MACE) was similar between the two groups, suggesting comparable safety profiles.

These findings are consistent with previous studies highlighting the efficacy of both intracoronary verapamil and adenosine in managing the no-reflow phenomenon. For example, Afshar EJ et al. [3], demonstrated the effectiveness of intracoronary epinephrine in improving coronary flow in no-reflow cases, aligning with our observations of verapamil's benefits. Similarly, Kiani SS et al. [11], reported successful outcomes with verapamil in refractory no-reflow cases, supporting our results and suggesting a potential preference for verapamil in clinical scenarios requiring significant improvement in coronary perfusion. The COAR trial by Khan KA et al. further underscores the efficacy of adenosine, though our study indicates that verapamil may offer slight advantages in specific settings [6].

Limitations

The study has several limitations that must be considered. The observational design, with treatment decisions made at the discretion of the treating cardiologist rather than through randomization, introduces potential selection bias. Although the sample size of 150 patients is sufficient for assessing primary outcomes, it may constrain the generalizability of the findings, especially regarding secondary outcomes like microvascular resistance (IMR) and endothelial function (FMD). The relatively short six-month follow-up period may not capture long-term effects and complications associated with these pharmacological agents. Additionally, reliance on angiographic assessments alone may not fully encompass the complexity of the no-reflow phenomenon.

CONCLUSION

This study highlights the effectiveness of both intracoronary verapamil and adenosine in managing the no-reflow phenomenon among normotensive

patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Our findings indicate that while verapamil offers a modest advantage in enhancing myocardial perfusion and reducing microvascular resistance, both agents are proven to be effective and safe for this clinical scenario. This underscores the need for clinicians to carefully consider these options based on individual patient characteristics and clinical contexts.

AUTHORS' CONTRIBUTION

QNUA, MAR, SHAS, SUS, SKUS, AA, and NA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. QNUA, MAR, SHAS, SUS, SKUS, AA, and NA: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Acknowledgment: None.

REFERENCES

1. Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. Eur Heart J. 2001;22(9):729-39.
2. Çelik İE, Öztürk S, Yarlıoğlu M, Barutçu O, Akgün O, Duran M, et al. The Association Between Atherogenic Index of Plasma and No-Reflow Phenomenon in Acute Coronary Syndrome. Anatol J Cardiol. 2023;27(12):712-9.
3. Afshar EJ, Samimisedeh P, Tayebi A, Hassani NS, Rastad H, Yazdani S. Efficacy and safety of intracoronary epinephrine for the management of the no-reflow phenomenon following percutaneous coronary interventions: a systematic-review study. Ther Adv Cardiovasc Dis. 2023;17:17539447231154654.
4. Kaul S. The "no reflow" phenomenon following acute myocardial infarction: Mechanisms and treatment options. J Cardiol. 2014;64:77-85.
5. Naing KA, Li L, Su Q, Wu T. Adenosine and verapamil for no-reflow during primary percutaneous coronary intervention in people with acute myocardial infarction. Cochrane Database Syst Rev. 2013;(6):CD009503.
6. Khan KA, Qamar N, Saghir T, Sial JA, Kumar D, Kumar R, et al. Comparison of Intracoronary Epinephrine and Adenosine for No-Reflow in Normotensive Patients With Acute Coronary Syndrome (COAR Trial). Circ Cardiovasc Interv. 2022;15(2):e011408.
7. Saood Y, Salman A, Khan M, Asim M. Comparison Of Intracoronary Epinephrine To Standard Treatments Alone For Refractory Coronary No-Reflow In STEMI Patients Undergoing Primary Percutaneous Coronary Intervention. Biol Clin Sci Res J. 2023;2023:277.
8. Saif M, Amin MU, Khan HS, Maken GR, Aziz Z, Janjua AF, et al. Comparison of intracoronary verapamil vs adenosine for restoration of coronary blood flow post percutaneous coronary intervention (PCI) in patients with no-reflow. Pak Arm Forces Med J. 2020;70(Suppl-4):S833-37.
9. Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet Public Health. 2020;5(9):e475-83.
10. Jafari Afshar E, Samimisedeh P, Tayebi A, Shafiabadi Hassani N, Rastad H, Yazdani S. Efficacy and safety of intracoronary epinephrine for the management of the no-reflow phenomenon following percutaneous coronary interventions: a systematic-review study. Ther Adv Cardiovasc Dis. 2023;17:17539447231154654.
11. Kiani SS, Nadeem A, Chauhdry AA, Farahe A, Shafique HM, Ashraf W, et al. Treatment of Refractory No-Reflow in Cardiac Catheterization Laboratory; Role of Intracoronary Verapamil (A Case Report). Pak Arm Forces Med J. 2022;72:S543-6